UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/560,829	03/07/2006	Fumihiko Ishikawa	4456-0105PUS1	6864

2292 7590 06/15/2010
BIRCH STEWART KOLASCH & BIRCH
PO BOX 747
FALLS CHURCH, VA 22040-0747

EXAMINER	
SCHULTZ, JAMES	

ART UNIT	PAPER NUMBER
1633	

NOTIFICATION DATE	DELIVERY MODE
06/15/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/560,829	ISHIKAWA ET AL.	
	Examiner	Art Unit	
	JD SCHULTZ, PhD	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 February 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-7,9-24,27,34-37 and 39-48* is/are pending in the application.

4a) Of the above claim(s) *5,7,9-24,27,35,37 and 45* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,6,34,36 and 39-44* is/are rejected.

7)☒ Claim(s) *46-48* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *see action*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

Please note that the examination of this application has been transferred to primary examiner James D. Schultz, whose contact information appears at the end of this communication.

Applicant's response filed February 24, 2010 has been considered. Rejections and/or objections not reiterated from the previous office action mailed August 25, 2009 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Election/Restrictions

Newly submitted claim 45 directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: The newly submitted claim is drawn to a method of making a transgenic mouse according to claim 1. However, methods of making a transgenic mouse are considered to be directed to a group that lacks unity of invention with the elected group, i.e. the transgenic mouse itself. The transgenic mouse of claim 1 is not considered to share a special technical feature with methods of making that mouse, since the transgenic mouse of claim 1 is not considered to comprise a contribution over the prior art in view of the art rejections cited herein. Accordingly, the technical feature shared amongst the groups is not considered to be special (i.e. a contribution over the prior art) and unity of invention is lacking.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claim 45 is withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

This application contains claims 5, 7, 9-24, 27, 35, 37, and 45 drawn to an invention nonelected with traverse in the reply filed on January 29, 2008. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Priority

Applicant's filing of a certified copy of an English translation of Japanese patent application JP -2003-171240 is acknowledged. However, it is noted that the translated Japanese patent application does not appear to reference the instantly claimed SCID/IL2rg null mouse. Accordingly, priority to this application is denied. Should applicants disagree, applicants are invited to point out with particularity by page and line number where support for the claimed IL2rg null mouse exists in the priority document.

Information Disclosure Statement

The information disclosure statements (IDS's) submitted on February 24, 2010 and December 16, 2009 were filed before the mailing date of the instant first action on the merits. The submissions are in compliance with the provisions of 37 CFR 1.97. Accordingly, the

information disclosure statements have been considered by the examiner, and signed and initialed copies are enclosed herewith.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2, 4, and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ishikawa et al. (Exp Hemat., May 2002. 30:5 488-494)), in view of mouse strain NOD.Cg-*Prkdc*^{scid}IL2rg^{tm1Wjl}/SzJ (Stock 005557, Jackson Laboratory). This rejection was previously set forth on pp. 5-6 of the Office action dated January 13, 2009, is maintained for reasons of record, and is re-iterated as follows:

The claims embrace a newborn NOD/SCID/IL2rg-null mouse into which human cord blood hematopoietic cells have been transplanted, and which is able to generate T cells from said human cells.

Ishikawa et al. describe long-term xenogeneic engrafting of cord blood human hematopoietic cells into newborn NOD/SCID/β2-microglobulin deficient mice (Title and Abstract; limitation of claims 1, 4 and 34). Further describing multilineage engraftment, and that high levels of engraftment were primarily by T cells (first column, p. 490 and Figure 1). With reference to previously published results by Kollet et al., the authors additionally state because

the duration of engraftment was relatively short, backcrossing onto other strains of mice may be needed for longevity, constituting breeding of the immature immunodeficient mouse (limitation of claim 2).

While Ishikawa et al. do not describe their graft recipient mice as NOD/SCID/IL2rg-null, such was known in the prior art. It should be noted that the instant specification indicates that the NOD/SCID/IL2rg-null mice are NOD.Cg-*Prkdc*^{scid}IL2rg^{tm1Wjl}/Sz, from Jackson Laboratory (Example 6, p. 23).

The product description for stock no. 005557, discloses NOD.Cg-*Prkdc*^{scid}IL2rg^{tm1Wjl}/Sz mice as commercially available from the Jackson Laboratory, and further states that the mice carry mutations for combined immune deficiency and IL2 receptor gamma deficiency, lack mature T cells, B cells and functional NK cells, leading to better engraftment of human hematopoietic stem cells.

The teachings of Ishikawa et al. and Jackson Laboratory product stock no. 005557 are both directed to engraftment of human hematopoietic cells in immunodeficient mice. Therefore, it would have been *prima facie* obvious for a person of ordinary skill in the art to utilize the NOD/SCID/IL2rg-null mouse in the transplantation assay described by Ishikawa et al. with a reasonable expectation of success, at the time of the instant invention. A person of skill in the art would have been motivated to utilize the NOD/SCID/IL2rg-null mouse for engraftment, as a matter of design choice, said design choice amounting to combining prior art elements according to known methods to yield predictable results. Applicants should note that the *KSR* case forecloses the argument that a specific teaching, suggestion, or motivation is required to support a finding of obviousness. *KSR International Co. v. Teleflex Inc.*, 550 U.S.-, 82USPQ2d 1385

(2007).

Claims 1, 2, 6, 36 and 39-44 are rejected under 35 U.S.C. §103(a) as being unpatentable over Ishikawa et al. (Exp Hematol., May 2002. 30:5 488-494), in view of mouse strain NOD.Cg-*Prkdc*^{scid}IL2rg^{tm1Wjl}/SzJ (Stock 005557, Jackson Laboratory) as applied to claims 1, 2, 4, and 34 above, and further in view of Olive et al. (Immunol. Cell Biol. 76:520-525, 1998). This rejection was first set forth on pp. 6-7 of the Office action dated January 13, 2009, is maintained for reasons of record to claims 1, 2, 6, and 36, is newly applied to added claims 39-44, and reiterated as follows:

The claims embrace a newborn NOD/SCID/IL2rg-null mouse into which mature human hematopoietic cells have been transplanted, and which is able to generate IgG immunoglobulin from said human cells.

Ishikawa et al. teach long-term xenogeneic engrafting of cord blood human hematopoietic cells into newborn NOD/SCID/β2-microglobulin deficient mice (Title and Abstract). Further teaching multilineage engraftment, that included cells bearing the CD19 pan-specific B cell marker (Table 1, p. 492). The product description for stock no. 005557, discloses NOD.Cg-*Prkdc*^{scid}IL2rg^{tm1Wjl}/Sz mice as commercially available from the Jackson Laboratory

While neither Ishikawa et al. or Jackson Laboratory product description for stock no. 005557 describe detecting IgG in the recipient newborn mice, the production of human IgG in xenografted immunodeficient mice was well known in the prior art. Olive et al. describe the successful engraftment of human peripheral blood lymphocytes in SCID mice, determined by measurement of human IgG in mouse sera, that continued to increase for 8 weeks, in addition to

T cell engraftment in lymphoid tissues (Title and Abstract; limitation of claims 6 and 36); thus curing the deficiency of IgG in Ishikawa et al. and product no. 005557.

Ishikawa et al. state that the number of cells that were planted per newborn mouse is less than the larger graft size previously reported in earlier studies (second column, p. 493), thus providing the motivation to use newborn mice instead of the 8 week old mice utilized by Olive et al.

The teachings of Ishikawa et al., product stock no. 005557 and Olive et al. are all directed to engraftment of human hematopoietic cells in immunodeficient mice. Therefore, it would have been *prima facie* obvious for a person of ordinary skill in the art to combine their respective teachings and to introduce human hematopoietic cells into newborn NOD/SCID/IL2rg-null mice to produce human T cells and IgG, with a reasonable expectation of success, at the time of the instant invention. A person of skill in the art would be motivated to use the newborn immunodeficient mouse of Ishikawa et al. for human hematopoietic cell engraftment, because such would require a smaller graft size.

Response to Arguments:

At the outset, it is noted that applicants are correct in indicating that the reference of Ishikawa et al. was improperly cited as having been published in the American Journal of Transplantation. In fact, the intended reference is that cited as citation "CA" on applicants IDS filed December 15, 2005,. In addition, applicants also correctly noted that the IL-2rg null mouse was improperly referenced as Stock No. 00557, when in fact, the correct Stock No. is 005557. These errors are regretted, and applicant's indication of the correct citations is appreciated.

Applicants have argued that the mouse strain 005557 cited in the Office Action was not developed until 2005, after the priority date of the claimed invention. Applicants have provided an article and catalog information to support this claim. It is thus argued that mouse strain 005557 is not prior art, and based on the assertion that Ishikawa and Olive taken alone or together do not teach NOD/SCID/IL2rg-null mice, the rejection of claims 1, 2, 4, ,6, 34 and 36 as being unpatentable over Ishikawa in view of mouse strain 005557 (and further in view of Olive for claims 1, 2, 4, and 34) should be withdrawn.

This argument has been fully considered, but is not convincing. While it is acknowledged that applicant-provided documents from Jackson Laboratory's website indicate that the IL2rg null mouse identified as Stock No. 005557 (and recited in at least claims 1 and 2) was described in a publication dated "Summer 2005", this is not an indication that it cannot be relied upon under 35 USC 102 as part of the instant obviousness rejection. 35 USC 102 recites (in part, emphasis added):

> A person shall be entitled to a patent unless –
>
> (a) **the invention was known or used by others in this country,** or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

It is noted that the instant specification at page 23, lines 17 and 18 describes the IL2rg null mouse used in the instantly claimed invention as being available from Jackson laboratories. Since the inventors were aware of the availability of this mouse for purchase, the IL2rg null mouse is considered to have been known or used by others at the time of applicants invention, meeting the criteria for its citation at least under 35 USC 102(a) as part of the instant obviousness rejection.

Applicants argue that claims 39-44 recite "antigen-specific human IgG, IgM and IgA" or "the amount of antigen-specific human IgG in the serum of the mouse." Applicants assert that none of the cited art references teach the generation of antigen-specific immunoglobulins, as recited in claims 39-44. While does it is agreed that the combination of references do not explicitly teach the generation of antigen specific immunoglobulins, this argument is not convincing. Applicants are reminded that the claim is not to a method of generating antigen specific immunoglobulins, but rather to a transgenic mouse that is an IL-2rg null mouse. This transgenic mouse is considered to be unpatentable in view of the instantly cited prior art. It is maintained that a mouse so made would naturally generate such immunoglobulins. Indeed, if the claimed mouse did not naturally generate these immunoglobulins in the claimed quantities, there would be sufficient reason to question the enablement of the instant claims. Accordingly, generation of the claimed immunoglobulins resulting from the presently claimed transgenic mouse is considered to constitute no more than an intended result that would naturally flow from a making a transgenic mouse that is an IL-2rg null mouse.

Claim 45 is drawn to a method of producing a NOD/SCID/IL2rg-null mouse transplanted with human-derived hematopoietic stem or precursor cells, wherein the method comprises irradiating an immature NOD/SCID/IL2rg-null mouse, and transplanting human-derived hematopoietic precursor cells or mature hematopoietic cells into the irradiated mouse. Applicants argue that Ishikawa teaches away from engrafting human cells into NOD/SCID mice, where the mice are conditioned using irradiation prior to introduction of human-derived hematopoietic stem or precursor cells. However, this claim has been withdrawn as being dependent upon a non-elected invention and arguments thereto are considered moot.

Applicants argue that claims 46-48 recite ratios of human-derived antibody- generating cells to recipient- derived antibody-generating cells in various tissues of the claimed mice, and that Ishikawa teaches that NOD/SCID/β2-microglobulin null mice show better engraftment than NOD/SCID mice. Applicants argue that based on the teachings of Ishikawa, it is unexpected that the NOD/SCID/IL2rg-null mouse strain shows higher levels of engraftment when compared with the NOD/SCID/β2-microglobulin null mice. Applicants point to table 2 at page 26 in support. This argument is considered convincing in regards to these claims, but no others. The rejection is accordingly maintained.

Allowable Subject Matter

Claims 46-48 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

Applicant's addition of new claims necessitated the new ground(s) of rejection against these claims presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JD SCHULTZ, PhD whose telephone number is (571)272-0763. The examiner can normally be reached on 8:00-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/JD SCHULTZ, PhD/
Primary Examiner, Art Unit 1633